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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 14, 2003. Currently, claims 42-73 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments and the amendments to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bidwell (Technique, Vol. 2, No.2, pages 93-100, 1990).

Bidwell et al. (herein referred to as Bidwell) teaches a method for rapidly allotype matching based upon PCR for human HLA-DR/Dw allotype. Bidwell teaches that HLA-DR and DQ matching is now generally undertaken as a clinical prerequisite for renal and bone marrow transplantation. Bidwell teaches that many polymorphisms at the DNA level exist which allow DNA typing to become more widely used as an adjunct or alternative to serological tests (page 94, col 1). Bidwell teaches that the HLA-DR/Dw

allotype method is useful for matching donor and patient in the selection of living related or unrelated volunteer donors for bone marrow transplantation (page 98, col 2).

Bidwell does not specifically teach performing a transplant upon finding a match of HLA-DR/Dw allotypes.

However, it would be prima facie obvious to one skilled in the art, at the time the invention was made to have performed the allotype matching method of Bidwell prior to performing a transplant. Upon determining the patient and the donor are a match for allotypes, it obvious to perform the transplantation in order to save the life of the patient. The patient which is to receive the transplantation would have been analyzed for their HLA-DR/Dw allotype following being identified as having a need for surgery. While the exact date for transplant surgery may be dependent upon finding a suitable match, upon finding the suitable match, it follows that a surgery would be performed. Unless, the patient had been identified for surgery, the test would have been needless and the matching of allotypings would be unneeded. Therefore, following an allotype assay it would have been obvious to perform the transplant if a match was found.

If the allelotyping of Bidwell is performed prior to surgery, as required by the claims, and it is determined that the transplant is not an appropriate match, then the surgery can be aborted and the risk for complications be eliminated. Therefore, there would be no risk for complications during said surgical procedure because there would not be a surgical procedure. It is noted that Claim 55 has no requirement that the "surgery must be scheduled". The specification states "the 'perioperative' period begins when surgery is first contemplated (e.g. when the patient is scheduled for

surgery) and ends when recovery from surgery is complete (e.g., when the services of a treating clinician are no longer required)". Therefore, the term perioperative as provided in the specification clearly encompasses when surgery is first contemplated.

Therefore, the claims which require selecting conditions, i.e. transplant matches, by assaying two or more nucleic acid genetic markers in two or more genes, prior to a surgical procedure would have been obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

The response traverses the rejection. The response asserts that the Examiner is in error. This argument has been reviewed but is not convincing because the amendments to the claims have overcome the previous rejection and necessitated the instant rejection. Thus for the reasons above and those already of record, the rejection is maintained.

4. Claims 42-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or

CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent.

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who

have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of masitive markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees

the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1 gene for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

Moreover, given the teachings of Hoon that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica

Scandinavica, La Du, Pharmacogenetics, Evans or Poort . Given the state of the art with relation to known markesr and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are

associated with MH would indicate to the anesthesiologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization to 5 or more mutations is not considered inventive and no evidence has been presented that the marker selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Response to Arguments

The response traverses the rejection. The response filed January 14, 2003 asserts that the cited art fails to establish prima facie obviousness. The claims have been amended to recite testing two or more nucleic acid markers. The response also

argues that it is "improper to combine Miller with any other art." The response continues that "since the primary reference cannot be properly combined, there is no prima facie showing of obviousness." Moreover, the response asserts that the examiner's burden has not been met with clear and convincing evidence in the form of "anything other than the Examiner's conclusory guesses." Additional arguments by the response include, "the examiner has concocted an argument for rejection on the basis of obviousness by coupling assertions of the invention's clear-cut and undisputed utility, with the incorrect, unsupported and conclusory guesses-in-hindsight about what an ordinary artisan "would have clearly recognized' or "would have been motivated to do". The response asserts that the "examiner cannot rely on gut feelings or personal beliefs no matter how strongly the Examiner holds these convictions." This argument has been thoroughly reviewed, but is not found persuasive. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the inoperability of the prior art must be supported by evidence, not argument. The response has provided no technical reasons why the ordinary artisan would not have been motivated to have assayed for genetic mutions prior to surgery which are known to be associated with consequences during a

surgical procedure. The ordinary artisan would have had a reasonable expectation of success for assaying for genetic markers prior to surgery. Finally, the ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided.

The response previously asserted that the combinations fail to establish a prima facie case of obviousness by the correct legal standard (page 10-14 of response filed July 8, 2002). The argument has been thoroughly considered and reviewed, however is not persuasive. The invention is drawn to testing patient before they have surgery for genetic variations which are known to have adverse effects and complications. Regardless of whether the test is viewed as not cost effective for broad application for all patients, it remains obvious to sample individuals before surgery for know mutations which affect surgical outcomes. The response submits several declarations and papers in which they attempt to demonstrate that the ordinary skilled artisan would not and does not recognize the benefits of the present invention. As addressed previously, the application for a grant entitled "Perioperative Genomic Profiles" to the Anesthesia Patient Safety Foundation (APSF) and was rejected by a panel of experts because "the state of the art teaches that such methods should not be carried out". Based upon the committees excerpt, the committed states that "the committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the values equation the committee members considered the study might improve the quality but the cost could be very high". While applicants are arguing

that the art is not routinely doing perioperative analysis, this is not the standard for obviousness. As provided by the statute of 103,

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The statute does not provide that cost is a factor in considering non-obviousness. The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious, but the committee rather appears to be indicating that they do not think that the idea is a cost effective study. The committee has states that "as anesthesia practice has moved toward determining the ratio or quality to cost, this study seems to be going in the opposite direction". This statement is directed to the economical benefits of sampling individuals prior to surgery not the obviousness of studying individuals prior to surgery. Furthermore, the factors considered when determining whether to fund a particular study are completely different than the factors considered to determine that an invention is legally patentable. Grants are often funded because they offer an immediate use, return on value or information that the community may build upon. These are not the criteria which must be met to obtain a patent or to show non-obviousness of the prior art references. The response argues that "this objective evidence of non-obviousness, confuses the fact of non-obviousness ("t would take the issue of patient safety in a new direction"), with the reasons for non-obviousness i.e. cost, confidentiality, ethics. The examiner agrees that the reasons, i.e.

cost effectiveness, etc. are immaterial to the finding of non-obviousness, therefore, the reasons given in the grant study are not material to the finding of non-obviousness.

The response provides three references directed to the proposition that routine perioperative testing is unnecessary. First, Gregroy teaches that value of routine preoperative screening tests for healthy infants and children has been questioned. Gregory teaches that "routine preoperative hemoglobin or hematocrit determinations have been recommended in the past, and have been or still are required by law in some jurisdictions. However, there are a few data to support the practice of subjecting every healthy child to a painful fingerprick or venipuncture." (page 184, col 1). While this passage illustrates that individuals may be questioning the need for blood tests prior to surgery many clinicians continue to sample blood and others are required to by law. Therefore, public policy deems it important to perform preoperative blood analysis. Similarly, Kirby teaches that routine laboratory screening tests are not cost-effective and are often inefficient. While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided. While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about the perioperative genetic testing.

The response cites Hopkins to support, "the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the

molecular genetics of MH concludes that DNA-based testing for MH is precluded and not desirable". The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting perioperative course of action. The claims are not drawn to diagnosing MH. Furthermore, the reference of Hopkins provides as much enabling disclosure as the instant application.

The response does not specifically address Quane who explicitly teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." This statement provides motivation to the ordinary artisan to sample prior to treatment with anesthetics which trigger MH.

The second declaration of Kirk Hogan, filed July 8, 2002, has been thoroughly considered, but found not persuasive. The declaration asserts that the state of the art has not tested subjects for genetic markers during the perioperative period. The declaration reviews a Practice Advisory for Preanesthesia Evaluation: A report by the American Society of Anesthesiologist Task Force on Preanesthesia Evaluation". The declaration asserts that no perioperative genetic testing of any kind is advocated, discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness. The response has selected certain passages from the evaluation which do not appear to represent the full teachings of the reference. The Practive Advisory for preanesthesia evaluation states that the study is intended to assist decision-making in areas of patient care, but

not intended as guideline, standards or absolute requirements. The evaluation may be "adopted, modified or rejected according to clinical needs and constraints (abstract). Moreover, preoperative tests may be indicated for various purposes including discovery or identification of a disease or disorder that may affect perioperative anesthetic care. It is noted that MH as taught by Quane is a disorder which will affect preoperative anesthetic care. Therefore, the reference does not appear to support the assertion that preoperative care precludes the testing of genetic markers. "The Task Force agrees that preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management. The indications for such testing should be documented and based on information obtained from medical records, patient interview, physical examination and type and invasiveness of the planned procedure" (page 490, col 1-2). Moreover, the Task force "believes that there is insufficient evidence to identify explicit decision parameters or rules for ordering preoperative tests on the basis of specific clinical characteristics" (page 490, col 1-2). Note 4, states that "selective preoperative tests (i.e., tests ordered after consideration of specific information obtained from sources such as medical records, patient interview, physical examination and the type of invasiveness of the planned procedure and anesthesia) may assist the anesthesiologist in making decisions about the process of preoperative assessment and management (page 493, col. 1). Therefore, based upon the teachings of the reference as a whole, the reference does not state that preoperative tests should not be done.

Thus, for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. **No claims allowable.**

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Brandt et al (Human Molecular Genetics, Vol. 8, No. 11, pages 2055-2062, 1999) teaches that 21 RYR1 mutations have been identified which account for more than 50 of the families with susceptibility to MH. Brandt teaches that the genetic testing may be used to determine whether individuals are likely to have MH.

B) Ciccone et al (herein referred to as Ciccone) teaches that "In anaesthesia, our preoperative assessment includes prescribed medications and allergies to drugs. We also consider factors, either directly or indirectly, which may influence responses to drugs, such as age, genetic history, metabolic phenotype,..." (page 255-256).

C) Monnier et al (herein referred to as Monnier) teaches a novel mutation in CACLN1A3 which segregate perfectly with the MHS phenotype in a French family. The substitution of an Arg-His at residue 1086 results in the transition of A for G3333.

D) Jensen et al (Acta Anaesthesiologica Scandnavica, Vol 39, page 150-156) teaches that patients with abnormal BchE often have prolonged apnoea following succinylcholine. Jensen teaches that on should not try to treat the block, but rather keep the patient anaesthetized and ventilated till the usually clinical criteria for full

recovery are present. Further, when a clinician is faced with a patient with an apparent abnormal response to succinylcholine, the use of a nerve stimulator is urged.

E) Masterson et al (Br. J. of Anaesthesia, Vol 77, No. 5, page 569-571, 1996) teaches that patients which are likely to mount excessive cytokine responses after surgery may be tested. "Such tests may help anaesthetists to predict outcome or the need for postoperative intensive care. They may also allow us to select the most appropriate anaesthetic, in terms of its ability to modulate cytokine activity, for each patient.

F) Caplan teaches numerous costs of adverse outcomes for anesthesia-related deaths. Among these costs is not only the economic costs, but also non-economic costs.

G) Larson et al (herein referred to as Larson) teaches the preoperative testing for a T to C transition in the codon for amino acid 85 of the beta globin gene. The individual was tested for an unstable Hb variant resulting in congenital hemolytic anemia which has an increased affinity for oxygen. Larson teaches that chronic hemolysis may result in cholelithiasis requiring cholecysterctomy. Perioperative management of this congenital hemoglobinopathy by partial-echange erythrocytapheresis to prevent introperative tissue hypoxia during general anesthesia and cholecystectomy. Lason describes the "perioperative management of a patient, with the unstable, high-oxygen-affinity Hb, HbBryn Mawr, who was deemed at risk for significant tissue hypoxia during general anesthesia and surgery".

H) Hecht et al (Anesth. Analg, Vol. 84, pg. 461-464, 1997) teaches a G1583A mutation in CACNL1A3 which is associated with HypoPP. Hecht also teaches that HypoPP has been identified as a disorder that can predispose a patient to the syndrome of MH which the risk of triggering skeletal muscle contraction and rhabdomyolysis, together with earlier reports of flaccid paralysis aggravated by surgery and general anesthesia, appear to favor regional anesthesia in this population whenever feasible (abstract). Hecht also teaches that MH susceptibility associated with HypoPP and of hypokalemia elicited by regional anesthesia suggests that hybrid anesthetic techniques be avoided (pg. 462, col. 2).

I) Korte et al (Clin. Chem. Lab. Med, Vol. 36, No. 4, pg. 235-240, 1998) teaches to establish a possible "perioperative reference range" for thrombin generation prothrombin fragment F1+2 and fibrin degradation markers were measured (abstract). Korte also teaches that preoperative determination of molecular markers would be helpful in identifying a group of patients at high risk for intraoperative disorder of hemostasis by exclusion of low risk patients (abstract). As seen in Table 2 and Table 3, the results of the detection assay for the two genetic markers were observed (pg. 237).

J) Brandt et al (Hum. Mol. Genetics, Vol 8, No. 11, pg 2055-2062, 1999) teaches screening of approximately 105 MH families for mutations. Despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is

not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2).

K) De Stefano et al (New England J. Med, Vol 341, pg 801-806, 1999) teaches screening for two point mutations, one in F 5 Leiden and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
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June 24, 2003

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